REMARKS

Reconsideration of this application, in view of the following remarks, is respectfully requested.

Entry of this amendment is respectfully requested as applicants submit that it will place the claims in a condition for allowance or in a better form for subsequent appeal.

I Status Of The Claims

Claims 4-7 and 16 have been canceled without prejudice Claims 1, 2, 18, and 19 have been amended to (i) limit the linker moieties recited therein to substituted or unsubstituted alkanoyl, substituted or unsubstituted alkenoyl or *(ortho or para)* carbonyl-substituted aryl, and (ii) limit the X group to oxygen. Claim 24 has been amended to correct a minor typographical error.

Applicants reserve the right to prosecute the subject matter deleted from claims 1, 2, 18, and 19, and the subject matter of claims 4-7 and 16, in one or more continuation application(s).

New claims 25 and 26 have been added. Support for claim 25 may be found, for example, in the specification at page 15, lines 5-10 (product of the fourth reaction sequence), and page 16, line 31-33 (the intermediate compound prepared in method A before hydrogenation gives the title compound). Support for claim 26 may be found, for example, in the specification at page 17, lines 1-25 (the product of Example 1, Method B).

Claims 1-3, 8-15, 17-20, and 22-26 are pending in this application, and are currently at issue.

The issues raised by the Examiner in the Office Action are summarized and addressed below.

II Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-20 and 22-24 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner maintains that the specification, while being enabling for compounds wherein phosphocholine is directly linked to steroids, is not enabling for attachment through the multitudes of linkers and moieties defined for X.. The Examiner asserts that it is unclear if the multitude of compounds covered by claims 1-9 could be prepared, and even if they could, it is unclear whether they would retain the required drug efficacy. With respect to preparation of the claimed compounds, the Examiner asserts that the specification provides no guidance at all as to how the various linkers and X moieties are attached to the various drugs claimed, and that the only working example in the specification is the attachment of a specific steroid with direct linkage to phosphocholine (not through a linker or an X moiety). The Examiner concludes that in the absence of a broad basis of support in the specification with regard to what linker and X moiety may be attached to what drug the claims must be limited to drugs directly attached to the phosphocholine.

Claims 4-7 and 16 have been cancelled, rendering the rejection of these claims moot.

With respect to pending claims 1-3, 8-15, 17-20, and 22-24, this rejection is not believed to be well taken, and is respectfully traversed.

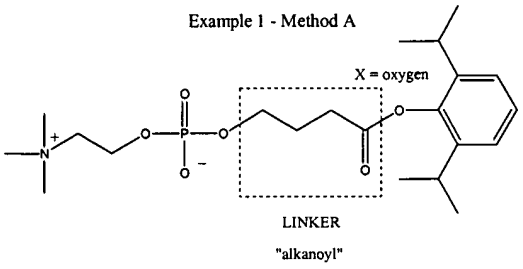
The presently pending claims are directed to compounds wherein the linker moiety is substituted or unsubstituted alkanoyl, substituted or unsubstituted alkenoyl, or *(ortho or para)* carbonyl-substituted aryl, and the X group is oxygen.

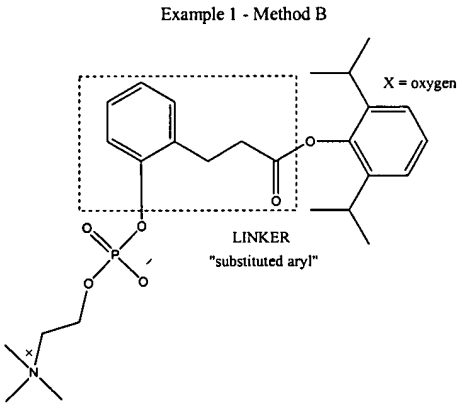
Contrary to the Examiner's assertions, the presently claimed compounds wherein X is oxygen and the linker is alkanoyl, alkenoyl, or substituted aryl are fully enabled by the specification.

The Examiner's attention is directed to pages 14 and 15 of the specification, wherein synthetic routes for preparing the claimed drug-X-linker-therapeutic agent compounds are described. A claimed compound can be enabled without disclosing working examples of the

preparation of the compound. "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." M.P.E.P. ¶2164.02.

Moreover, the Examiner's assertions respecting the working examples of the present specification (Example 1, Methods A and B, set forth at pages 16 and 17) are incorrect. Example 1 discloses the synthesis of the following two compounds:





As can clearly be seen, the phosphocholine moiety in the compounds exemplified in Example 1, methods A and B, is not directly attached to the therapeutic agent (2,6-diisopropylphenol), as incorrectly asserted by the Examiner. Rather, the compound prepared by Method A contains an alkanoyl linker (and oxygen as the X group), and is, in fact, the subject matter of claim 17. The compound of Method A is prepared by hydrogenation of the corresponding alkenoyl linker containing intermediate (see page 16, lines 32-33 of the specification). The compound exemplified in example 1, Method B contains a carbonyl substituted aryl linker (and oxygen as the X group), and is the subject matter of new claim 26.

Therefore, compounds wherein X is oxygen and the linker is alkanoyl, alkenoyl, or carbonyl substituted aryl are fully enabled by the specification. Moreover, the compounds covered by present claims 17, 25, and 26 (the synthesis of each of which is dislcosed in Example 1, Methods A and B) are clearly enabled by the present specification.

Contrary to the Examiner's assertion, the specification does provide guidance as to how the linkers and X moieties are attached to the therapeutic agent. The Examiner's attention is directed to page 4, lines 1-10 of the specification, wherein the nature of the attachment is clearly set forth. Moreover, the nature of the linkers useful in the present invention is clearly defined at pages 5, line 1 to page 10, line 1 of the specification. Examples of therapeutic agents are clearly set forth in the section entitled "Examples of therapeutic agents which benefit from a phosphocholine agent" at pages 10 and 11 of the specification.

In view of the above, applicants submit that the specification is sufficiently enabling for the presently pending claims, and respectfully request that the rejection be withdrawn.

III Claim Rejections Under 35 U.S.C. § 103

Claims 1-20 and 22-24 have been rejected under 35 U.S.C. § 103 as obvious over Chasalow (U.S. Patent No. 5,830,432, "Chasalow"). The Examiner asserts that Chasalow discloses drug derivatives of phosphocholine and methods of increasing the aqueous solubility of biologically active agents by conjugating them to phosphocholine moieties. The Examiner was not persuaded by the arguments set forth in our June 25, 2004 response that Chasalow only teaches attachment via a carboxyl functionality persuasive, and cites Example 5 of Chasalow (which assertedly shows attachment of DHEA to homophosphocholine via an alcohol functionality). Furthermore, the Examiner asserts that it would have been obvious to use any active agent with a reasonable chance of success in view of the suggestion in Chasalow that the method is applicable to any active agent.

This rejection is not believed to be well taken, and is respectfully traversed.

Contrary to the Examiner's assertions, Chasalow is completely silent with respect to using a linker wherein the X moiety is attached to the therapeutic agent via an alcohol functional group.

In the Abstract, Chasalow states that the methods disclosed therein are for "increasing the aqueous solubility and bio-availability of bioactive agents having a free-carboxyl group...", and that "the target drugs have a carboxy group as the site of linkage to the phospholipid." See col. 3, lines 59-61. Moreover, at col. 2, lines 38-42, Chasalow asserts (emphasis added):

> The present invention is directed to increasing the bioavailability and/or aqueous solubility of pharmaceutically active agents, **specifically by conjugation of such agents via a free carboxy group** to a phospholipid . . .

Chasalow only teaches attaching the therapeutic agent to a linker via a carboxyl functionality attached to an amine functionalized linker (thereby actually forming an amide -C(O)-NH- attachment between the linker and the therapeutic agent). See the last structures given at cols. 5 and 8 of Chasalow.

Contrary to the Examiner's assertion, in Example 5 of Chasalow, the therapeutic agent (DHEA) is attached directly to phosphocholine, thereby producing DHEA-3-phosphocholine (see col. 11, line 62). No linker is used between the phosphocholine and the DHEA.

Therefore, Chasalow is completely silent with respect to a conjugate wherein the therapeutic agent is attached to the linker moiety via an alcohol functionality, and does not teach or suggest using a linker attached via an alcohol functionality to the therapeutic agent.

Indeed, Chasalow teaches away from the presently claimed compounds whereby the therapeutic agent is attached to a linking moiety via an alcohol, stating, at col. 2, lines 38-42, that the [Chasalow] invention is directed to increasing the bioavailability and/or aqueous solubility of

pharmaceutically active agents, **specifically by conjugation of such agents via a free carboxy group** to a phospholipid (emphasis added).

Therefore, one of ordinary skill in the art would have had no reasonable expectation of success that conjugates could be formed by linking the therapeutic agent to the phosphocholine by attachment of the agent to a linker via an alcohol functionality.

Moreover, the only drugs disclosed in Chasalow are seratrodast, isbrogrel, indomethacin, ridogrel, salicamide, aspirin, probenecid, tenidap, daltroban (see col. 2, lines 1-13, and col. 4, lines 33-34) and DHEA (Example 5). Chasalow provides no motivation or suggestion to prepare phosphocholine derivatives of drugs other than these specific therapeutic agents, such as the sedative 2,6-diisopropyl phenol (propofol), as required by present claims 16, 17, 22, 25, and 26 . These phosphocholine derivatives would have been at best "obvious to try," without a reasonable expectation of success. However, as the Examiner knows, "obvious to try" without reasonable expectation of success is not the standard under 35 U.S.C. § 103. The proper test requires determining what the prior art would have led the skilled person *to do*.

The Examiner's attention is directed to the Federal Circuit's decision in *In re O'Farrell*, 853 F.2d 984, 7 USPQ2d 1673 (Fed. Cir. 1988). In particular, the court noted:

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

One of ordinary skill in the art would simply not have been motivated, based on the disclosure of Chasalow, to prepare the claimed compounds of formula (I) wherein a water insoluble steroid, anesthetic or sedative agent, such as propofol, is linked to a phosphocholine moiety via an alcohol functional group.

Accordingly, the present claims are not obvious over Chasalow. Applicants respectfully request that the rejection be withdrawn.

In view of the above amendments and arguments, the pending claims in this application are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to enter this Amendment, and to pass this application to issue.

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Respectfully submitted,

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